Fatal toxicity associated with antidepressant use in primary care

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SUMMARY

Background. *New selective serotonin reuptake inhibitors (SSRIs) are perceived to be much safer in use than older tricyclic antidepressants (TCAs). However, previous assessments of association with fatal toxicity were made too soon after the introduction of the new drugs to permit accurate estimation.*

Aim. *To determine the level of association of antidepressant drugs with fatal poisoning in the treatment of depression.*

Method. *National data for England and Wales for three years (1993 to 1995) for fatal poisonings associated with antidepressants were obtained and, together with national primary care data on prescribing, were used to calculate fatality association by antidepressant drug.*

Results. *There were substantial variations between drugs in the level of association with fatal poisoning. Assuming an average treatment episode lasted three months, one fatality is associated with 11 800 treatment episodes of antidepressant use (95% CI = 11 120 to 12 580) when only single substance fatalities are considered. For SSRIs as a group the association was one in 411 800 (95% CI = 243 300 to 1.34 million) and for TCAs one in 8130 (95% CI = 7650 to 8670). However, for one of the newer TCAs, lofepramine, the single substance fatality rate associated with its use was one in 233 700 (95% CI = 124 500 to 1.89 million), which is not statistically significantly different from the SSRIs (P = 0.35).*

Conclusions. *Estimated death rates associated with specific antidepressants should be compared with caution because drugs may be used selectively in patients with differing severity of depression. The proportion of these fatalities that could be prevented by switching to safer antidepressants is unclear when so few deaths are recorded as accidental; when there is intent to do self-harm the potential for switching to other means is unknown. However, this approach to relative toxicity may remain the best available since it is unlikely that a randomised trial will ever be conducted with a large enough sample size to obtain experimental data. Fatalities from antidepressant poisoning are very rare but if safety is paramount then lofepramine or an SSRI are justifiable treatment choices.*

Keywords: *mental health; antidepressants; fatal toxicity; SSRIs; TCAs.*

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Introduction

IT is now a decade since fluoxetine (Prozac), the first of a new class of antidepressants called selective serotonin reuptake inhibitors (SSRIs) to receive widespread use, was licensed in the United Kingdom. Over most of this period a debate has continued concerning the effectiveness, tolerability, safety, and cost-effectiveness of SSRIs compared with older, established tricyclic and related antidepressants. An important argument for the routine firstline use of SSRIs has been their apparent safety in overdose, although previously data have been inadequate to explore the importance of this claim. Previous assessments of the relative toxicity of antidepressants were made too early in the life cycle of the SSRIs to make accurate estimation possible. An analysis of toxicity-related events in 1990 found no recorded fatalities associated with SSRI ingestion.[1]

This issue was recently revisited by a North of England Guidelines Group assessing the use of antidepressants in primary care[2] and in this context a comprehensive profile of fatal toxicity associated with antidepressant ingestion was developed. Calculation of toxicity association had two strands: first, an assessment of the volume of use of antidepressants (by drug) and secondly, a summary of recorded fatalities associated with antidepressant ingestion, whether ingested alone or in combination with other substances, and whether recorded as accidental, deliberate, or of unknown intent. In Britain, these data are routinely recorded on coroners' reports and informed by the statutory post-mortem required for a poisoning-associated fatality.

Method

Poisoning fatality records for England and Wales for three years (1993 to 1995) naming ingestion of antidepressants were obtained directly from the Office for National Statistics. These were aggregated to obtain both counts of single- or multiple-ingested substance fatalities and by reported intent. Multiple ingestion is defined here to include the taking of any medicinal substance in addition to an antidepressant (this may include another antidepressant) but excludes alcohol.

In England, the Prescription Pricing Authority (PPA) reimburses all National Health Service (NHS) primary care-prescribed antidepressants. PPA data list the cost and number of units of each antidepressant by drug, brand, form, and dose, so that if an average daily dose is used it is possible to estimate the total volume of patient years of treatment purchased. Average daily doses applied are those indicated by World Health Organisation Defined Daily Dose data.[3] These are not necessarily those recommended in the British National Formulary (BNF)[4] and may not always reflect the average maintenance dose in adults but provide a consistent point of reference (Table 1). Quarterly data supplied by the PPA were aggregated to calculate the total volume of use for each antidepressant over three years (1993 to 1995). English prescribing data were multiplied by a factor of 1.06 to adjust for the population of England and Wales.

When calculating rates of drug-associated fatal poisonings to compare differences between drugs it is necessary to identify not just numbers of deaths but extent of patient exposure, hence the use of prescribing data to calculate the volume of use of drugs.

Table 1. Classification and defined daily dose of prescribed antidepressants.

Classification	Defined daily dose (mg)
Tricyclic	
Amitriptyline	75
Amoxapine	150
Clomipramine	100
Desipramine	100
Dothiepin	75
Doxepin	100
Imipramine	100
Lofepramine	105
Nortriptyline	75
Protriptyline	30
Trimipramine	150
Tricyclic-related	
Maprotiline	100
Mianserin	60
Trazadone	300
Viloxazine	200
MAOI[a]	
Phenelzine	30
Isocarboxazid	20
Tranylcypromine	20
RIMA[b]	
Moclobemide	300
SSRIs	
Citalopram	20
Fluoxetine	20
Fluvoxamine	150
Paroxetine	20
Sertraline	75
SSRI-related	
Nefazodone	400
Venlafaxine	150
Other	
Flupenthixol	2
Trytophan	1500

[a]Monoamine oxidase inhibitors; [b]Reversible inhibitor of monamine oxidase type A.

However, patient years of treatment are likely to underestimate patients treated and it is necessary to make an assumption about the average duration of treatment. This follows, since a clinician may wish to know how likely an episode (rather than a year) of treatment is to be associated with a fatal poisoning. The guideline group for which the toxicity index was originally developed concluded that, pragmatically (if not ideally), three months was the most realistic assumption. Data for person years of treatment and three-month treatment episodes are presented here.

Each drug has a number of treatment episodes (n) and a number of associated fatalities (f). The probability (p) of a fatal poisoning is the simple proportion f/n and its confidence intervals are given as $p \pm 1.96se$, where the standard error (se) is estimated as $[p(1-p)/n]^{1/2}$.

Results

It is estimated that nearly three million patient years of treatment with antidepressants were reimbursed by the NHS in primary care in England and Wales during 1993 to 1995. This volume of treatment suggests that about 2% of the population were receiving treatment for depression during the study period. This is plausible when set against a reported prevalence of about 5% for neurotic and depressive illness in general practice for England and Wales,[5] where not all patients would receive an antidepressant. Volume of use for specific drugs is shown in Table 2.

During this period there were 1005 single substance antidepressant associated fatalities and 1459 fatalities involving an antidepressant alone or in combination with another substance (Table 2). Nearly 70% of all antidepressant-associated poisoning fatalities involved a single-ingested antidepressant. Approximately half of all fatal poisonings are identified as deliberate and about 15% are recorded as accidental.

Fatal poisoning associated with antidepressant use increased by 5% each year while use of antidepressants increased by 11% in 1994 and a further 16% in 1995. Across all three years, antidepressant poisoning consistently accounted for approximately 17.5% of all recorded fatal poisonings associated with drugs, medicaments, and biological substances.[6,7]

When adjusted for volume of use there were substantial variations between drugs in the level of association with fatal poisoning (Table 3). Overall, the average fatality rate per episode of treatment associated with single-ingested antidepressant toxicity is 0.0000847. In other words, one fatality may be expected for every 11 800 episodes or every 2950 patient years of treatment (Table 4).

Tricyclic antidepressants generally feature substantial cardiovascular toxicity and a higher associated fatality rate (0.000123 per treatment episode, one fatality for every 8130 treatment episodes). SSRIs are relatively safe with a group fatality rate of 0.0000024 per treatment episode, one fatality for every 412 000 episodes. One second generation tricyclic antidepressant appears atypical: lofepramine features a fatality rate similar to the SSRIs of 0.0000043 per treatment episode, approximately one fatality for every 234 000 treatments, and statistically is not significantly different from the SSRIs as a group ($P = 0.35$ by Fisher's exact method, odds ratio = 1.76, 95% CI = 0.45 to 6.11 by Gart's exact method).

When comparing lofepramine and the SSRIs, a non-significant test result cannot be interpreted as proof of the absence of a difference in the rate of drug-associated fatality. However, it is possible to say that analysis of three years' national activity data has failed to estimate any such difference with precision.

Discussion

Estimated death rates associated with specific antidepressants are based on observational data and should therefore be compared with caution: higher death rates may be explained by trends in use of certain drugs with more severely depressed and co-morbid patient groups as well as by underlying pharmacological toxicity. Additionally, it is only possible to make reasonable estimates of toxicity where substantial use is made of specific drugs. Different assumptions are possible about the average length of treatment episode, and thus level of patient exposure, but analyses based upon using average treatment episodes of six months or one year do not alter qualitatively any of the results presented.

Caveats accepted, there remains a substantial range of toxicity associated with different antidepressants currently used in primary care. The SSRIs and lofepramine are associated with the smallest risk of fatal poisoning. It is uncertain whether fatalities could be significantly reduced by a policy of wide-scale switching to less toxic antidepressants as some substitution between

Table 2. Fatal poisonings in England and Wales (1993–1995) associated with antidepressants and volume of use.

	Single-ingested substance				Single- and multiple-ingested substance				Patient years of treatment
	n	Accidental	Deliberate	Unknown	n	Accidental	Deliberate	Unknown	
Amitriptyline	324	53	154	117	452	80	221	151	505 382
Amoxapine	6	0	3	3	10	1	6	3	3083
Citalopram	0	0	0	0	0	0	0	0	1174
Clomipramine	14	2	7	5	35	8	16	11	92 481
Desipramine	4	1	2	1	12	2	6	4	1631
Dothiepin	520	76	260	184	673	105	341	227	910 450
Doxepin	13	3	8	2	23	6	13	4	28 573
Fluoxetine	7	0	4	3	19	2	7	10	455 728
Flupenthixol	0	0	0	0	0	0	0	0	51 928
Fluvoxamine	0	0	0	0	6	2	3	1	19 740
Imipramine	57	9	26	22	80	15	37	28	78 474
Isocarboxazid	0	0	0	0	1	0	1	0	3786
Lofepramine	5	1	2	2	18	4	11	3	292 113
Maprotiline	0	0	0	0	1	0	0	1	5844
Mianserin	0	0	0	0	0	0	0	0	24 026
Moclobemide	1	0	0	1	5	1	1	3	11 536
Nefazodone	0	0	0	0	0	0	0	0	2314
Nortriptyline	6	1	1	4	30	8	13	9	19 613
Paroxetine	0	0	0	0	5	0	0	5	257 366
Phenelzine	3	0	1	2	5	1	2	2	22 714
Protriptyline	0	0	0	0	0	0	0	0	2599
Sertraline	1	0	1	0	4	0	4	0	89 664
Tranylcypromine	4	1	1	2	11	2	1	8	19 703
Trazadone	4	1	2	1	11	1	7	3	23 736
Trimipramine	22	6	9	7	32	7	15	10	38 599
Tryptophan	0	0	0	0	0	0	0	0	690
Venlafaxine	0	0	0	0	0	0	0	0	2225
Viloxazine	0	0	0	0	0	0	0	0	246
Not specified	14	3	3	8	26	9	6	11	-
Tricyclic	971	152	472	347	1365	236	679	450	1 972 997
Tricyclic-related	4	1	2	1	12	1	7	4	53 852
MAOI	7	1	2	4	17	3	4	10	46 203
RIMA	1	0	0	1	5	1	1	3	11 536
SSRI	8	0	5	3	34	4	14	16	823 671
SSRI-related	0	-	-	-	0	-	-	-	4540
Other	0	-	-	-	0	-	-	-	52 618
Overall	1005	157	484	364	1459	254	711	494	2 965 416

fatal means may be expected.[1] A conservative assumption might be to argue that single-ingestion accidental poisoning fatalities (152 during 1993 to 1995) in the tricyclic subgroup might be reduced by changing the prescribed antidepressant. It would seem unduly optimistic that all multiple-ingestion poisonings (1365 during 1993 to 1995) could be prevented when only 17% are recorded as accidental.

These data could be interpreted in different ways. One view might be that no risk of toxicity is acceptable and that tricyclic antidepressants should no longer be prescribed. Alternatively, an association with poisoning in these drugs of one in 8130 treatment episodes might be viewed as an acceptably small risk when the scope for prevention by substitution remains so unclear. Our interpretation is that antidepressant fatalities are very rare but when safety is a prime concern then lofepramine or an SSRI, on current evidence, are rational treatment choices.

References

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Table 3. Fatality rate per 10 000 treatment episodes associated with antidepressant ingestion in England and Wales (1993–1995).

	Single-ingested substance			Single- and multiple-ingested substance		
	P[a]	95% CI[b]		P[a]	95% CI[b]	
Amitriptyline	1.603	1.428	1.777	2.236	2.030	2.442
Amoxapine	4.866	0.973	8.759	8.110	3.086	13.135
Citalopram	-	-	-	-	-	-
Clomipramine	0.378	0.180	0.577	0.946	0.633	1.260
Desipramine	6.133	0.125	12.142	18.399	7.998	28.800
Dothiepin	1.428	1.305	1.551	1.848	1.708	1.988
Doxepin	1.137	0.519	1.756	2.012	1.190	2.835
Fluoxetine	0.038	0.010	0.067	0.104	0.057	0.151
Flupenthixol	-	-	-	-	-	-
Fluvoxamine	-	-	-	0.760	0.152	1.368
Imipramine	1.816	1.345	2.287	2.549	1.990	3.107
Isocarboxazid	-	-	-	0.660	0.000	1.955
Lofepramine	0.043	0.005	0.080	0.154	0.083	0.225
Maprotiline	-	-	-	0.428	0.000	1.266
Mianserin	-	-	-	-	-	-
Moclobemide	0.217	0.000	0.641	1.084	0.134	2.033
Nefazodone	-	-	-	-	-	-
Nortriptyline	0.765	0.153	1.377	3.824	2.456	5.192
Paroxetine	-	-	-	0.049	0.006	0.091
Phenelzine	0.330	0.000	0.704	0.550	0.068	1.033
Protriptyline	-	-	-	-	-	-
Sertraline	0.028	0.000	0.083	0.112	0.002	0.221
Tranylcypromine	0.508	0.010	1.005	1.396	0.571	2.221
Trazadone	0.421	0.008	0.834	1.159	0.474	1.843
Trimipramine	1.425	0.830	2.020	2.073	1.355	2.791
Tryptophan	-	-	-	-	-	-
Venlafaxine	-	-	-	-	-	-
Viloxazine	-	-	-	-	-	-
Tricyclics	1.230	1.153	1.308	1.730	1.638	1.821
Tricyclic-related	0.186	0.004	0.368	0.557	0.242	0.872
RIMA	0.217	0.000	0.641	1.084	0.134	2.033
SSRI	0.024	0.007	0.041	0.103	0.069	0.138
SSRI-related	-	-	-	-	-	-
MAOI	0.379	0.098	0.659	0.920	0.483	1.357
Other	-	-	-	-	-	-
Overall	0.847	0.795	0.900	1.230	1.167	1.293

[a]Death rate (P) by fatal poisoning and associated with named antidepressants per 10 000 treatment episodes (see method section); [b]see method section; [c]no fatalities recorded.

Table 4. Treatment episodes per fatality associated with antidepressant ingestion in England and Wales (1993–1995): class effects.

	Single-ingested substance[a]			Single- and multiple-ingested substance[a]		
	Number of episodes	95% CI		Number of episodes	95% CI	
Overall	11 800	12 580	11 120	8130	8570	7730
Tricyclics	8130	8670	7650	5780	6110	5490
Tricyclic-related	53 850	2 691 000	27 200	17 950	41 340	11 460
RIMA	46 140	∞	15 590	9230	74 720	4920
SSRI	411 800	1 341 000	243 300	96 900	146 000	72 520
SSRI related	-	-	-	-	-	-
MAOI	26 400	101 900	15 170	10 870	20 720	7370
Other	-	-	-	-	-	
Sub-group analysis						
Lofepramine	233 700	1 893 000	124 500	64 910	120 700	44 400
Tricyclics (excluding lofepramine)	6960	7430	6550	4990	5270	4740

[a]Numbers of episodes and their confidence intervals are calculated as the inverse of the fatality rate per 10 000 episodes and its confidence intervals in Table 3.

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